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A Bioresorbable, Polylactide Reservoir for Diffusional and Osmotically Controlled Drug Delivery

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ABSTRACT The purpose of this study was to design and characterize a zero-order bioresorbable reservoir delivery system (BRDS) for diffusional or osmotically controlled delivery of model drugs including macromolecules. The BRDS was manufactured by casting hollow cylindrical poly (lactic acid) (PLA): polyethylene glycol (PEG) membranes (10 x 1.6 mm) on a stainless steel mold. Physical properties of the PLA:PEG membranes were characterized by solid-state thermal analysis. After filling with drug (5 fluorouracil [5FU] or fluorescein isothiocyanate [FITC]-dextran:mannitol, 5:95 wt/wt mixture) and sealing with viscous PLA solution, cumulative in vitro dissolution studies were performed and drug release monitored by ultraviolet (UV) or florescence spectroscopy. Statistical analysis was performed using Minitab®(Version 12). Differential scanning calorimetry thermograms of PLA:PEG membranes dried at 25°C lacked the crystallization exotherms, dual endothermal melting peaks, and endothermal glass transition observed in PLA membranes dried at -25°C. In vitro release studies demonstrated zero-order release of 5FU for up to 6 weeks from BRDS manufactured with 50% wt/wt PEG (drying temperature, 25°C). The release of FITC dextrans of molecular weights 4400, 42 000, 148 000, and 464 000 followed zero-order kinetics that were independent of the dextran molecular weight. When monitored under different concentrations of urea in the dissolution medium, the release rate of FITC dextran 42 000 showed a linear correlation with the calculated osmotic gradient($\Delta\pi$). PEG inclusion at 25°C enables manufacture of uniform, cylindrical PLA membranes of controlled permeability. The absence of molecular weight effects and a linear dependence of FITC-dextran release rate on$\Delta\pi$ confirm that the BRDS can be modified to release model macromolecules by an osmotically controlled mechanism.

Key Words: Zero-order, Reservoir, PLA, Osmotic Delivery, Thermal Analysis.

INTRODUCTION

Implantable delivery systems that provide zero-order drug delivery have the potential for maximizing efficacy while minimizing dose frequency and toxicity [1,2]. Numerous zero-order delivery systems have been developed that are either the matrix type, in which drug is dissolved or dispersed in a solid polymeric matrix [3-9], or the reservoir type, in which a solid drug core is contained in a rate-controlling polymeric membrane [10-11]. Reservoir delivery systems provide potential advantages over matrix systems because filling a preformed reservoir eliminates exposure to heat, organic solvents, or shear stresses that cause inactivation of unstable molecules in matrix systems. Since 1975, osmotic pressure has been used in drug delivery systems as a mechanism to deliver drugs at zero-order rates. A recent review summarizes the

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various developments since that time [12]. However, most osmotically controlled systems are non-bioresorbable. We propose to develop a bioresorbable implantable device that could deliver both low and high molecular weight (MW) drugs at zero-order rates using osmotic pressure as the rate-controlling mechanism.

The polyhydroxy acids poly (lactic acid) (PLA) and poly (lactides-co-glycolides) (PLGA) are bioresorbable polymers widely used in drug delivery. We elected to use PLA, known to be impermeable to drug molecules, to fabricate membranes of controlled permeability by incorporating polyethylene glycol (PEG). The overall hypothesis of this research is that a reservoir system can be manufactured from a bioresorbable, rate-controlling membrane consisting of PLA and PEG to deliver model drugs including macromolecules by a diffusional, osmotically controlled mechanism. To confirm the mechanism of drug release, dissolution studies were performed using model drugs. Specifically, 5 fluorouracil (5FU) was used to prove diffusion control, while fluorescein isothiocyanate (FITC) dextrans of molecular weights 4400, 42 000, 148 000, and 464 000 g/mol were used to confirm osmotic control.

THEORY

Principle of Operation

The design of the bioresorbable reservoir delivery system (BRDS) consists of a cylindrical PLA:PEG membrane enclosing a solid drug core (**Figure 1**). The concentration of PEG and the manufacturing conditions for the PLA:PEG membranes were carefully selected to obtain membranes of controlled permeability. In dissolution media, water diffuses into the BRDS and dissolves a fraction of the drug, thus forming a concentration or osmotic gradient. While the concentration gradient favors drug diffusion into the dissolution.medium, the osmotic gradient draws water into the BRDS, forming an internal hydrostatic pressure that "pumps" drug solution out of the device.

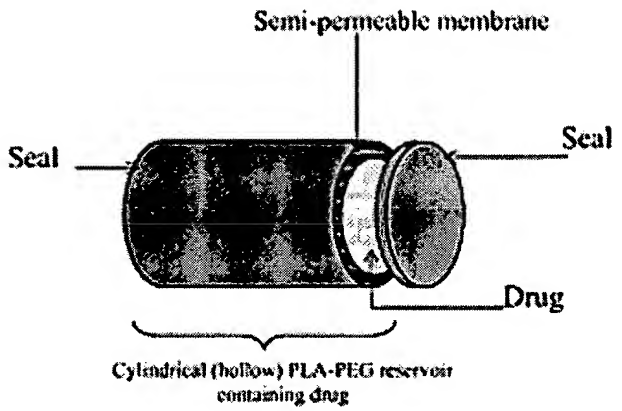

Figure 1. Illustration of the poly (lactic acid (PLA):polyethylene glycol (PEG) bioresorbable reservoir delivery system.

Under conditions in which both mechanisms operate simultaneously, the mass of drug released per unit time (dm/dt) is given by the sum of the diffusional and osmotic contributions [13]:

$$\frac{dm}{dt} = \frac{A}{h}k'\Delta\pi S + \frac{A}{h}k''\Delta C \qquad (1)$$

where A and h = area and thickness of the film, k' = the product of mechanical permeability and reflection coefficient, = osmotic gradient across the PLA:PEG membrane, S = the saturation solubility of the drug in the dissolution medium, k" = the solute permeability coefficient, and Δ C = the concentration gradient. If the drug concentration inside the reservoir is maintained at saturation under sink conditions, equation 1 reduces to

$$\frac{dm}{dt} = \frac{A}{h}k'\pi_s S + \frac{A}{h}k''S \qquad (2)$$

where π_s is the osmotic pressure of a saturated drug solution.

Diffusion-controlled drug release for sparingly water-soluble drugs

For sparingly soluble drugs, $\pi_s \approx 0$, and drug release from the BRDS occurs by diffusion (equation 3).

$$\frac{dm}{dt} = \frac{A}{h} k'' S \qquad (3)$$

When release occurs by diffusion through aqueous-filled pores within the membrane, the solute permeability coefficient, k", is given by $\varepsilon D_m / \tau$ where ε= the porosity, τ = the tortuosity, and $\mathbf{D_m}$ = the drug diffusivity. For a diffusion-controlled device, therefore, drug release rates depend both on permeability of the membrane and on physical properties of the drug.

Osmotically controlled drug release by including an internal osmotic agent

If a drug with low osmotic potential is added to the BRDS containing an excess of an osmotic agent, such as mannitol, we hypothesized that the hydrostatic pressure generated inside the device would "pump" both the osmotic agent and drug from the device. Under these conditions, the drug release rate will be governed by equation 1, and zero-order release can be achieved if both $\Delta \pi$ and $\Delta X\epsilon$ are maintained constant. For macromolecular drugs that exhibit low aqueous diffusivities as a result of their large molecular size, the contribution of the diffusion mechanism may be ignored, and therefore equation 1 reduces to

$$\frac{dm}{dt} = \frac{A}{h} k' \Delta \pi S \qquad (4)$$

Under these circumstances, the drug release will depend on the saturation solubility of the osmotic agent and not the drug (equation 4) and, as a consequence, will be independent of the physical properties of the drug. The advantage of this design is that the BRDS would deliver drugs of various molecular weights at a constant rate.

Membrane properties

Equation 1 holds true only if the membrane area and thickness remain constant. Preliminary studies in our laboratory have demonstrated that PLA can be readily cast as thin films (~ 0.1 mm). Further, the polymer degrades by bulk hydrolysis that begins 2 to 3 weeks of incubation after an initial lag-phase [14]. However, PLA is hydrophobic and impermeable to hydrophilic molecules [15-17]. To enhance permeability of PLA membranes, the effect of PEG inclusion, drying time, and membrane thickness on PLA permeability were studied and optimized using factorial design methodology.

Selection of model drugs and osmotic agent

The selection of drug and osmotic agent was based on their saturation solubility, which determines their ability to maintain a saturated solution inside the BRDS. The total volume of the PLA reservoir was calculated to be 15.4 μLs (π x 0.07 x 0.07 x 10 cm^3). Based on aqueous solubilities, 2.8 mg of mannitol and 1.88 mg of 5FU were required to saturate this volume at room temperature [18]. As 10 mg of mannitol and 20 mg of 5FU could be packed into the BRDS, about 70% to 90% of the incorporated osmotic agent or drug will be released at zero-order.

MATERIALS AND METHODS

Materials

Poly (L- lactide) (Eco-PLA™ 520 series) was a generous gift from Cargil, Inc (NE). Methylene chloride was obtained from Fisher Scientific (Pittsburgh, PA). Hexane was obtained from Burdick & Jackson Division (MI). Polyethylene glycol (MW 3350), 5FU, all FITC dextrans (MW 4400, 42 000, 148 000, 464 000), D- mannitol, and gelatin (Type A, from porcine skin) were obtained from Sigma Chemical Company (MO). The buffer salt - potassium phosphate monobasic and sodium phosphate dibasic anhydrous - were obtained from Mallinckrodt AR ® (NJ).

Methods

Manufacture of the delivery systems

Cylindrical, hollow reservoir membranes were prepared by dipping a stainless steel mold with 1.6 mm

rods into a 10% wt/wt polymeric solution of various PLA:PEG ratios (100:0, 50:50). The rods were prelubricated first with Teflon and then with gelatin solution at 40°C. Membrane thickness was varied by dipping 2 or 6 times at regular 5- minute intervals. After drying, the mold was immersed in warm water for 4 to 12 hours to facilitate removal of the cylinders. The cylinders were then cut to 10 mm in length (total surface area ~ 1.1 cm^2), washed in warm water to remove gelatin, and vacuum dried at 37°C for 24 hours. The dried, hollow polymeric cylinders were filled with either 20 mg 5FU or 10 mg of a 95:05 wt/wt Mannitol-FITC dextran mixture. After filling, the cylinders were sealed with a viscous (15% wt/wt) solution of PLA in methylene chloride and air dried for 24 hours.

Factorial Design

A 3-factor, 2- level, factorial design with 2^3, or 8, trials was used (n = 5). The high and low values for the 3 independent variables are shown in **Table 1.** The thickness of the polymeric membranes was measured using a micrometer. Release rates of 5FU were determined as the responsible variable for each trial, and factorial analysis was performed using Minitab ® Version 12 (MINITAB Inc, PA) to calculate the significant main and interactive effects at $\alpha = 0.01$.

Molecular weight determination

The differential refractive index increment (dndc) for PLA was obtained using a Wyatt/Optilab DSP interferonic refractometer after calibration with saline solutions at concentrations of 0.3, 0.5, 0.7, 0.9, and 1.0 mg/mL. GPC studies were performed using a Shimadzu LC-6A high-performance liquid chromatography (HPLC) pump, a 100 µL sample loop, 2 Ultrastyragel® columns (internal diameter 7.8 mm, length 30 cm, particle size 7.0 µm, and pore sizes of 10^4 and 10^3Å) in series, a Dawn® DSP Laser Photometer for measuring light scattering, and the Dawn® DSP Interferonic Refractometer to determine concentration. The molecular weight of the sample was calculated using Astra software, version 4.70.07 (Wyatt Technology Corporation, CA), and was found to be 324 000 ± 41 700 g/mol.

Thermal analysis

Differential scanning calorimetric (DSC) thermograms were obtained using a Shimadzu DSC-50 differential scanning calorimeter fitted with a Shimadzu TA-50 data processor. The instrument was calibrated with indium standard (melting point, 156°C). Approximately 2 mg of each sample was crimped in an aluminum pan and heated at 10°C/min from 25°C to 200°C in an atmosphere of nitrogen (flow-rate, 20 mL/min). The midpoint, range, and specific heat change associated with glass transitions and the peak area of each observed exotherm or endotherm were monitored using thermal analysis software. Similarly, a Shimadzu TGA-50 thermogravimetric analyzer fitted with a Shimadzu TA-50 data processor was used to obtain thermograms from 2 mg samples heated at the same rate and temperature range as described above. The percent weight loss for each sample heated from 0°C to 200°C was plotted as a function of temperature and the onset and total weight loss for each sample was determined. Thermomicroscopic studies were carried out using a Mettler hot stage (model FP82HT) mounted on a Nikon OptiHot biological microscope fitted with a Mettler model FP90 central processor as the controller. All samples were heated at a rate of 10°C/min to 200°C, and phase transitions and loss of volatile components were observed using a 10X objective under polarized and unpolarized light.

Release studies

Differential dissolution studies were performed using screw-capped scintillation vials containing 20 mL of Sorensen's phosphate buffer, pH 7.4, agitated at 5 rpm in a horizontally shaking water bath at 37°C. The concentration of 5FU was determined at 265.7 nm using a Shimadzu ultraviolet (UV)-visible recording spectrophotometer (model UV 160 U). The concentration of FITC dextrans released was determined spectrofluorometrically using a Shimadzu RF5000U Spectrofluorophotometer at absorption and emission wavelengths of 492 and 512 nm.

Data analysis and optimization

a) Statistical designs and optimization: The results of the factorial design study were analyzed by factorial ana lysis to determine the significant main and.interactive effects of thickness, drying temperature, and PEG inclusion on permeability of the BRDS membrane. To determine the optimal PLA:PEG ratio for osmotic control, response surface designs with multiple response optimization was performed to minimize lag-times and maximize linear regression coefficients (R^2) for release of FITC-dextrans (MW 4400, 42 000, 148 000, 464 000) from PLA:PEG cylinders of weight ratio 90:10, 70:30, and 50:50. Both the factorial analysis and the optimization were performed using Minitab ® software. All designs were examined for statistical uncertainty, and the reported values are significant at $\alpha = 0.1$.

b) Confirmation of the osmotic mechanism: To prove that under osmotic control drug release rate will linearly depend on$\Delta\pi$ (equation 4), release of FITC dextran 42 000 was monitored with various concentrations of urea in the dissolution medium. As saturated solution of mannitol has an osmosity of 0.62 g/mol per liter [18], urea concentrations of 0, 15, 30.2, 45.4, and 60.5 g/L that correspond to osmosities of 0, 0.134, 0.271, 0.407, and 0.550 were used. Osmosity is defined as the molar concentration of a NaCl solution that has the same freezing point, or osmotic pressure, as the given solution [18].

RESULTS AND DISCUSSION

Thermoanalytical studies

Figure 2 shows the DSC thermograms of PLA and PLA:PEG membranes manufactured according to conditions described in **Table 1.** While the PLA:PEG membranes ab, abc, and ac showed an additional endothermal peak for PEG melting at 57.1°C, PLA membranes 1, b, bc, and c showed dual endothermal peaks for PLA melting as well as crystallization exotherms that corresponded to weight loss observed in thermogravimetric analysis (TGA) thermograms. The effect of drying temperature was observed as an endothermic glass transition for PLA membranes manufactured at -25°C (trials 1 and c) as opposed to a simple lowering in specific heat for membranes dried at room temperature (trials b and bc, **Figure 2**). PLA glass transition could not be detected in PEG-containing membranes due to masking by the PEG melting endotherm.

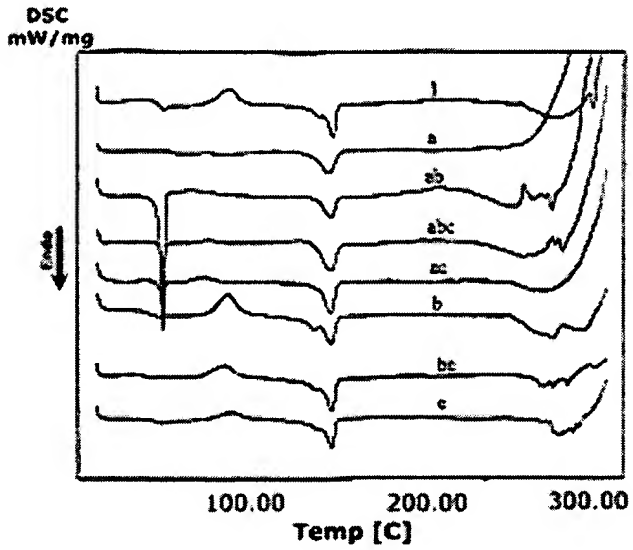

Figure 2. Differential scanning calorimetry (DSC) thermograms of poly (lactic acid (PLA) membranes manufactured under various conditions as documented in Table 1. (Key: 1, a, ab, abc, ac, b, bc, and c refer to manufacturing conditions listed in **Table 1**).

Table 1: Three factor, two level factorial design study.

Trial	PEG Content (% wt/wt)	Drying Temp (°C)	Membrane thickness (mm)
1	0	-25	0.07 ± 0.02
a	50	-25	0.07 ± 0.02
b	0	25	0.07 ± 0.02
c	0	-25	0.14 ± 0.03
ab	50	25	0.07 ± 0.02
bc	0	25	0.14 ± 0.03
ac	50	-25	0.14 ± 0.03
abc	50	25	0.14 ± 0.03

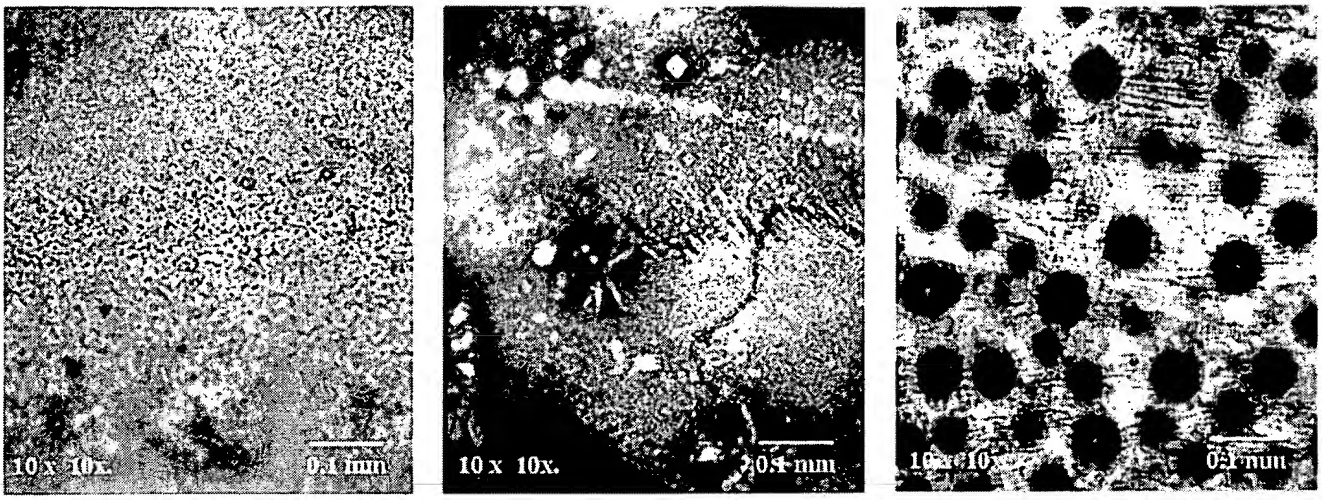

Figure 3. Effect of drying temperature and poly (lactic acid (PLA):polyethylene glycol (PEG) ratio on membrane morphology. (a) Trial 1, (b) trial b, (c) trial bc. (Key: 1, b, and bc refer to manufacturing conditions listed in **Table 1**).

Microscopic examination showed irregular film formation in PLA and PLA:PEG membranes manufactured at -25°C (**Figures 3a and 3b**]), whereas PLA membranes dried at 25°C showed dark circular regions indicating rapid evaporation of the organic solvent on drying (**Figure 4c**). PLA:PEG membranes dried at 25° C showed no visible imperfections and were used for all subsequent studies.

Diffusion-controlled drug release

The release kinetics of 5FU from the BRDS were linear ($R^2 > 0.90$) for all trials of the factorial design (**Figure 4**). Factorial.analysis showed that all the factors -PEG ratio (A), drying temperature (B), thickness (C), and the interaction factor (AB)-significantly altered membrane permeability. However, due to the heterogeneous structure of membranes manufactured at -2□°C and the difficulty of maintaining uniform thickness, PEG concentration was selected as the parameter to control PLA permeability for further studies.

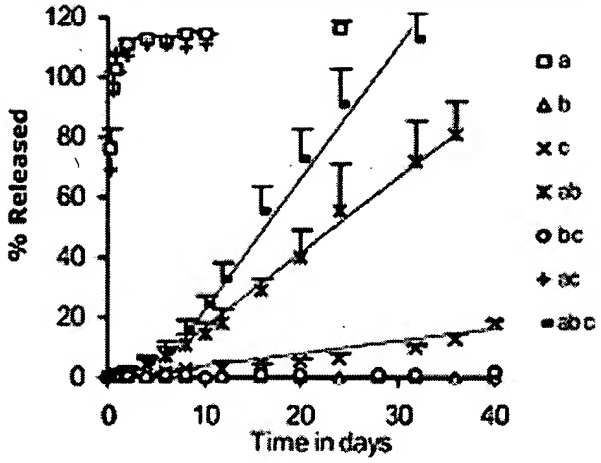

Figure 4 . Release kinetics of 5 fluorouracil (5FU) from the bioresorbable reservoir delivery system. (Key: a, b, c, ab, bc, ac, and abc refer to manufacturing conditions listed in **Table 1**).

Osmoticcally controlled drug release

About 60% to 80% of all FITC dextrans were released at zero-order rates of 10% to 30% per day, with R_2 values ranging from 0.88 to 0.98. **Figure 5** shows the effect of molecular weight and PEG ratio on (a) drug release rates expressed as percent per day; (b) zero-order character of drug release, expressed as linear regression coefficients (R^2) for the FITC dextran release-time curves; and (c) variance, expressed as sum of squares of standard deviation for drug release from each composition.

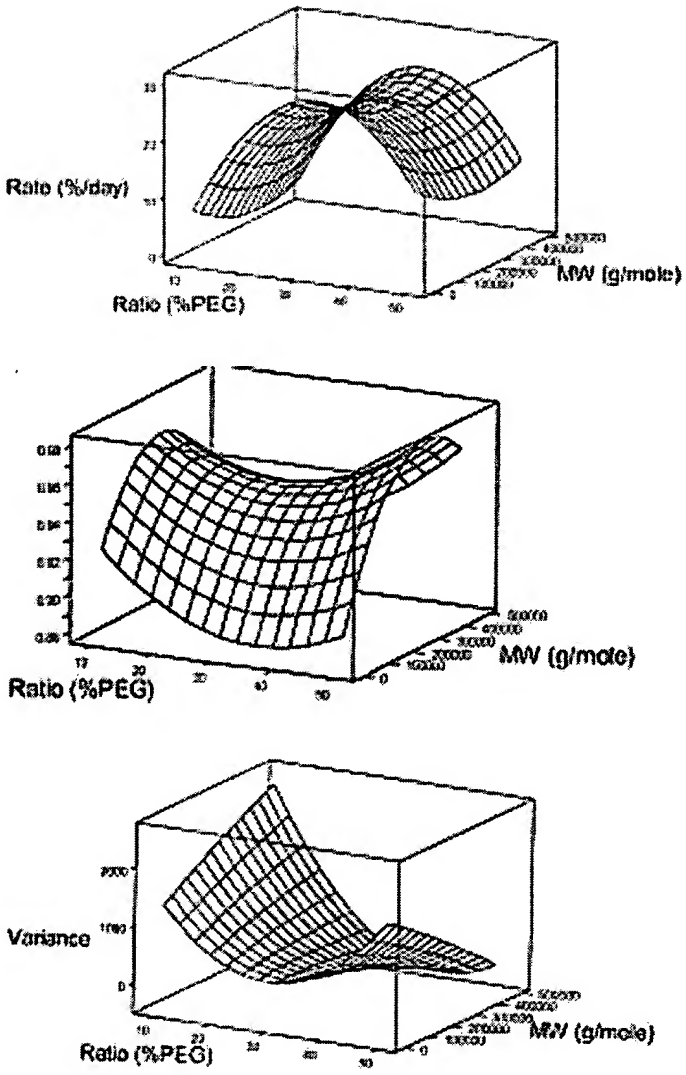

Figure 5. Effect of polyethylene glycol (PEG) ratio and drug molecular weight on (a) the release rate of fluorescein isothiocyanate (FITC) dextrans, (b) linear regression coefficients for drug release, and (c) variability in the FITC-dextran release data. (Key: Variability is expressed as sum of squares of standard deviation).

While the drug release rates and variance were unaffected by molecular weight, a significant increase in permeability and decrease in variance was observed in BRDS manufactured with 30% wt/wt of PEG (α = 0.1). Although the R^2 values were unaffected by PEG concentration, FITC dextrans of higher molecular weights showed higher R^2 values. Multiple response optimization showed that the optimal solution for minimizing variability, while maximizing R^2 value to

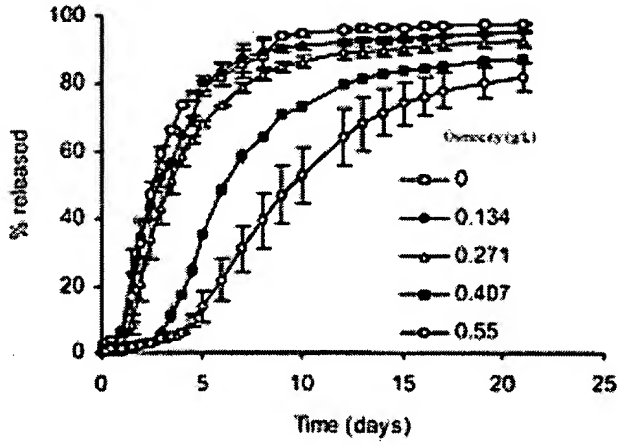

Figure 6. Effect of osmotic pressure on the release of fluorescein isothiocyanate (FITC) dextran 42,000.

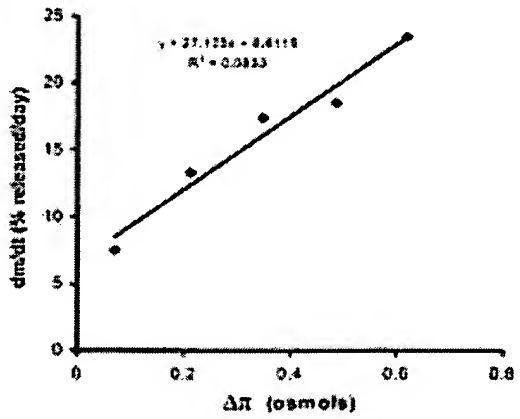

Figure 7. Effect of osmotic gradient on the release rate of fluorescein isothiocyanate (FITC) dextran 42 000.

achieve a target release rate of about 20% per day, was 45% wt/wt of PEG.

Figure 6 shows the release of FITC dextran (MW 42 000) from PLA:PEG 55:45 cylinders when incubated in a dissolution medium containing 0, 15, 30.2, 45.4, and 60.5 g/L of urea.

Drug release was associated with an initial lag-time that progressively increased with increasing urea concentration. A linear correlation was observed between the drug release rate, dm/dt, and the osmotic gradient $\Delta\mu$ (R^2 = 0.96), as shown in **Figure 7**.

The crystallization exotherms in PLA membranes were attributed either to cold crystallization resulting from solvent loss or rearrangement of PLA crystals, or to lower thermodynamic states due to increased polymeric mobility above the glass transition [19]. Bershtein and Egorov [19] state that the most common cause for multiplicity of the melting process is the reorganization and recrystallization of folded chain crystals during heating. The absence of exotherms and dual endothermic melting peaks in PLA:PEG membranes indicate that PEG incorporation improves the thermodynamic stability of PLA, and therefore, these membranes are less likely to undergo polymorphic transformation during storage. The endothermic glass transition observed for PLA films dried at -25°C is.characteristic of annealed polymers and may indicate crystal growth and microphase separation due the slow drying [11].

The diffusion-controlled zero-order release kinetics observed for the release of 5FU is in accordance with equation 3. Slow release rates for BRDS manufactured without PEG (trials c, b, and bc of the factorial design) confirm earlier findings that PLA is impermeable to hydrophilic compounds [15]. Rapid burst profiles for PLA:PEG 50:50 BRDS manufactured at -2

5°C (trials a and ac) indicate highly permeable or leaky membranes, as confirmed by thermoanalytical and microscopic studies. The optimal release for PLA:PEG 50:50 BRDS, manufactured at 25°C (trials ab and abc), shows that the controlled incorporation of PEG is necessary for the manufacture of uniform PLA membranes with controlled permeability. The zero-order release observed for 60% to 80% of all FITC dextrans indicate a significant osmotic component to drug release in this system. The absence of a molecular weight effect on release rates and a linear dependence of dm/dt on $\Delta\pi$ are in agreement with equation 4, confirming that the BRDS containing a 95:05 wt/wt mixture of mannitol:FITC dextrans functions as an osmotic pump. The higher R^2 values for FITC dextrans of higher molecular weight (**Figure 6b**) and a non-zero y- intercept for the dm/dt versus $\Delta\pi$ plot (**Figure 8**) indicate that a finite diffusion component exists in the BRDS and accounts for up to 6.6% of drug release.

CONCLUSIONS

The high molecular weight, low therapeutic window, and poor aqueous stability of most macromolecules pose numerous challenges to drug delivery. By eliminating manufacturing stress and providing a mechanism for zero-order release of macromolecules in the presence of excipients, the osmotically controlled BRDS may be used as a clinical and research tool for delivery of numerous drugs including macromolecules. The in vivo efficacy of the BRDS is currently being investigated for the continuous subcutaneous infusion of insulin (CSII) in rats with streptozocin-induced diabetes.

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